A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition

Sponsor Protocol Number: PIA-2020
Principal Researcher: Associate Prof Roger Clarnette

1 Would you like to take part in this clinical trial?

We would like to invite you to take part in our clinical trial. This is because you are a male or female, diagnosed with Alzheimer's Disease and aged between 18 and 84, and may therefore be eligible for this trial.

This document tells you about the trial and describes what will happen if you decide to take part. We strongly encourage you to read the information carefully. If there is anything you don't understand or want to know more about, please ask us. We will be happy to provide more information.

If you don't know what to ask, there are some questions to consider in the *Clinical trial participant information and consent form: Part A – General information*.

You might also want to talk to a relative, a friend or your General Practitioner before you make up your mind. If you decide to go ahead, we will ask you to sign the consent form (the last page of this document). We will give you a copy of the complete signed document to keep.

We wish to emphasise that participation in this research is completely voluntary. If you don't wish to take part, there is no obligation to do so. You will continue to receive the best possible care, irrespective of whether or not you agree to participate.

2 Why are we doing this research?

Before a new medicine can be approved for use in a particular disease, it is necessary to confirm that it is safe and effective. This is done by carrying out clinical research studies such as this one.

Curtin University is conducting this research project to test a potential drug for Alzheimer's Disease (AD), called Probucol (also known as Lorelco™).

Alzheimer's disease involves a decline in memory and thinking skills as a result of generalised degeneration of the brain. Recent research has found that this degeneration happens because of abnormal build-up of proteins (including a protein known as amyloid) in and around brain cells. Alzheimer's disease gets worse with time and there is no effective treatment for it.

Recent research has shown that Probucol (Lorelco™) appears to decrease inflammation of microscopic blood vessels in the brain called brain capillaries. These capillaries are important for maintaining brain function, cognition and memory. Probucol appears to do this because it reduces the blood vessel exposure to potentially toxic proteins. Probucol is also a very strong anti-oxidant (meaning it prevents or slows damage to cells). This suggests that Probucol (Lorelco™) may be effective in slowing the decline in memory and thinking skills in people with Alzheimer's disease.

The main goals of this study are to:

- To determine whether Probucol (Lorelco™) is effective for slowing the decline in memory and thinking skills in people with AD
- To evaluate whether Probucol (Lorelco™) improves quality of life in people with AD
- To examine the impact of Probucol (Lorelco™) on amyloid protein in people with AD
- To determine how safe and well tolerated Probucol (Lorelco™) is in people with AD

This is the first time Probucol will be tested for the treatment of cognitive decline due to mild/moderate Alzheimer's Disease. Lorelco™ is approved in Japan and other countries, including South Korea and China, for the treatment of high cholesterol. Probucol is not approved for the treatment of any diseases in Australia and hence Probucol is considered an experimental treatment. The risks associated with taking this drug are described in Section 13.

3 Do I have to take part?

No. It's your choice. If you don't wish to take part, you don't have to. If you decide to take part and later change your mind, you are free to withdraw at any stage. If you choose not to take part, or if you choose to take part and then later withdraw, you will still be able to access your usual medical care. Your choice will not affect your relations with those treating you, or with the Australian Alzheimer's Research Foundation.

If you do withdraw your consent during the clinical trial, the research team will stop collecting personal information from you. But they will keep the personal information they have collected up to that point. There is a good reason for this. Sometimes, the law requires it. It is also retained for accurate measurement as the trial results must include all the data actually collected.

Just to be clear on this point. We must keep and collect any information about you, up to the time you withdraw. **The Australian Alzheimer's Research Foundation** the institution conducting the trial, and Curtin University (the institution paying for this study - called a study "sponsor") have access to this information so they can check it is correct. If you do not agree with this then we cannot allow you to join the clinical trial.

4 What are the main steps in the study?

This study is being sponsored by Curtin University. It is being conducted at the Australian Alzheimer's Research Foundation and will enrol approximately 300 patients.

This research project involves 104-weeks (2 years) of repeat daily oral dosing of the study drug.

The procedures to be performed in this study are described below.

In this study, you will receive either Probucol (Lorelco™) or placebo. A placebo is a medication with no active ingredients and thus has no clinical effect. It looks like the real thing but is not. Probucol (Lorelco™) is provided as an oral capsule and will be referred to as the study drug throughout this document.

You will be allocated to receive either the study drug or the placebo drug using a computer-generated schedule. To avoid accidentally influencing the tests performed in the study, neither you nor the researchers will know which study medication you were assigned to, but don't worry, this information can be obtained in case of an emergency. Neither you nor the study doctor can choose what you receive.

The total maximum study duration for participants in this study is **112 weeks (2 years and 8 weeks),** including the screening period and follow-up visit.

You will be screened to determine your suitability to take part in the study within 24 days before receiving a dose of the study drug. You will need to attend clinic visits on weeks 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, and 104. One of the members of the clinical staff will call you on weeks 6, 20, 29, 47, 55, 73, and 81 to check on your health status and determine whether you have taken any other medication during this period. You will be asked to present to the clinic for a final study visit on week 108. This visit will be the end of your participation in this study. There are no overnight confinement periods for this study.

Before you can participate as a volunteer in this study, we first need to confirm that you are eligible to take part. Participation in this study is based on a number of criteria which are taken into consideration by the study doctor in order to make sure that the potential risks of your participation in this study are minimised as much as possible.

For this trial, we need the help of participants with Alzheimer's disease aged from 18 to 84. Participants must be willing to use highly effective contraceptive methods during their participation in this study. If you are selected to participate, the study doctor will advise you of the appropriate methods of contraception.

Additionally, in order for you to participate in this study, a study partner (partner/spouse/carer) is required to also consent to the minimum requirements of attending at least one screening visit, complete a questionnaire, and being available via phone or in person to provide information to the study as required, for the duration of the study. In the event the study partner withdraws from the study, you will be asked to nominate a new study partner. You will not be able to continue your participation in the study without a study partner.

Screening Visit (Day -24 to Day -1)

Before the start of any procedures associated with this study, you (and your study partner) will need to sign the consent form to document your agreement to participate in the study, to the study restrictions and procedures. You will be given as much time as required to ensure that you fully understand what is involved in the participation of this study. If you do consent to be involved in this study, you must be willing to cooperate with the directions of the study team.

If you consent to take part in the study, you will be asked to attend an appointment at the Australian Alzheimer's Foundation for an initial assessment (screening visit) and to have some tests to check that the study is suitable for you. Screening will be conducted within 24 days before starting study participation. It may take more than one day to complete all the study procedures. During screening, the below listed assessments will be performed. When results of the assessments performed are available, the site study staff will confirm whether the study is suitable for you. The expected duration for the screening visit is approximately 3.5 hours. During your appointment(s) you will be offered regular breaks and refreshments.

The following tests will be performed during screening:

- **Medical and Disease history:** A full medical history will be obtained, including pre-existing conditions, allergies, prior significant illnesses and surgical history. It may also include smoking history, substance use and/or alcohol intake, and any drug allergies. Demographic data including your age, gender, race and ethnicity will also be recorded.
- **Check of medications:** You will be asked whether you are taking any medications. This includes over-the-counter, prescription medications, contraception medication, herbal products, diet aids and hormone supplements.
- **Dietary Requirements**: Consumption of grapefruit or Seville orange (or products containing grapefruit or Seville orange) is not permitted within 7 days prior to the first of study drug and throughout the study.
- **Assessment of Alzheimer's Disease:** You will be asked to undergo a PET/MRI scan. This is an imaging test that allows your doctor to see different portions of your brain and how they have been affected by Alzheimer's disease. The scan uses a special dye containing radioactive tracers. These tracers are either swallowed or injected into a vein in your arm. This may take place on a different day to the other tests.
  You (and your study partner) will also undergo a number of assessments in which the investigator will assess a range of mental functions.
- **Physical examination:** You will be required to remove any thick clothing you have and open or lift your shirt to enable examination of your chest and abdomen. The following systems will be assessed: skin, head, ears, eyes, nose and throat, lymph nodes, heart, chest, abdomen and extremities, and a neurological examination (assessment of speech, cranial nerves, motor power, deep tendon reflexes, sensation, coordination and gait).

- **Vital sign measurements:** Blood pressure, respiration rate, heart rate and temperature. You will be required to be resting in a supine position (laying down flat on a bed on your back) for at least 5 minutes prior to and during vital signs measurements.
- **ECG:** You will undergo an electrocardiogram (ECG), three readings will be taken, which will assess the electrical activity of your heart. You will be required to remain supine for at least 5 minutes prior to the ECGs, and you will be unable to use any electronic devices, including mobile phones.
- **Blood samples:**
    - You will be provided with a pathology form for Clinical Labs Australia. Clinical Labs is located adjacent to the Australian Alzheimer's Research Foundation. A sample of blood (approximately 20 mL or 4 teaspoons) will be collected from a vein in your arm using a needle and syringe (venepuncture) and routine laboratory safety tests, including an assessment of how long it takes your blood to clot, will be performed. You may choose to have the blood sample taken on the same day as the other tests, or you may choose to have the blood sample taken on another day. You must arrive in a fasted state, having not consumed any food for at least 8 hours prior to completing the blood test (water is permitted though).
- **Urine samples:**
    - If you are a female of childbearing potential, your urine sample will also be used to test if you are pregnant. If a positive pregnancy test result is found, a second pregnancy test (blood) will be performed. If a positive pregnancy test is found, you will not be able to participate in the study.

The above tests, medical history and physical examination will determine whether you are suitable for participation in this study. Your history of **any** disease or disorder affecting any body system **must** be reported to the Study Doctor, and they will determine whether this excludes you from participating in the study. It is in your best interest to answer all questions completely and honestly. The study doctor will inform you if you can participate in the study.

Your General Practitioner will also be informed of your participation in the study. However, you can consent (or not) for your General Practitioner to provide details of your past medical history to the study doctor. It is not a requirement for participation that you consent to your general practitioner providing information to the study doctor.

Study Procedures

Pre-Baseline Visit (Weeks 1 to 3)

You will report to the Australian Alzheimer's Research Foundation], Suite 17/95 Monash Ave, Nedlands WA 6009. Your eligibility will be confirmed by checking that you still meet all the criteria for the study since screening. Ineligible participants will be sent home.

The following procedures will be conducted:

- **Medication use:** You will be questioned regarding any medication use since the screening assessment.
- **Assessment of Alzheimer's Disease:** One assessment will be performed to assess your mood.
- **Confirmation of eligibility**: The study doctor will review the assessment and test results to confirm you can still participate in the study.
- **Randomisation**: You will be randomised to your study treatment.
- **Dispensing of Probucol (Lorelco™) or Placebo**: Your study treatment will be provided to you for at-home dosing.

- **Dose administration:** One dose per day taken in the morning, with food. In the event that you miss a dose of medication, please take the capsule as soon as you remember. If more than 2 hours have passed since you were due to take the capsule, do not take the capsule that you missed. Resume taking the capsules as per usual at the next scheduled time. Do not double dose (take two capsules at once) if you have missed a dose. This may increase the chance of experiencing any side effects.

Baseline Visit 1 (Day 1, Week 3)

During your appointment you will be offered regular breaks and refreshments. The following procedures will be conducted:

- **Confirmation of eligibility**: The study doctor will review the assessment and test results to confirm you can still participate in the study.
- **Medication use:** You will be questioned regarding any medication use since the screening assessment.
- **ECG:** You will undergo an electrocardiogram (ECG), three readings will be taken, which will assess electrical activity of your heart. You will be required to remain supine for at least 5 minutes prior to the ECGs, and you will be unable to use any electronic devices, including mobile phones.
- **Blood samples:**

  You will be provided with a pathology form for Clinical Labs Australia. Clinical Labs is located adjacent to the Australian Alzheimer's Research Foundation. A sample of blood will be collected from a vein in your arm using a needle and syringe (venepuncture) and routine laboratory safety tests will be performed. Please ensure that you fast from food for at least 8 hours prior to your arrival (consuming water is allowed).
- **Assessment of Alzheimer's Disease:** One assessment will be performed to assess your memory and thinking skills
- **Dispensing of Probucol (Lorelco™) or Placebo**: Your study treatment will be provided to you for at-home dosing. An amount will be provided to last one week.
- **Dose administration:** One dose per day taken in the morning, with food. In the event that you miss a dose of medication, please take the capsule as soon as you remember. If more than 2 hours have passed since you were due to take the capsule, do not take the capsule that you missed. Resume taking the capsules as per usual at the next scheduled time. Do not double dose (take two capsules at once) if you have missed a dose. This may increase the chance of experiencing any side effects.
- **Adverse Reactions:** You will be monitored to check for any reactions to the dose and will be questioned about your health routinely throughout the day. Any other medications that you use will also be recorded.

Visits (Weeks 4, 5, 15, 26, 39, 52, 65, 78, 91)

The following procedures will be conducted:

- **Medical review** of your general health will be conducted and a physical exam may be performed if you are not feeling well, or your Study Doctor determines an examination is required.
- **Review of medications used**
- **Vital signs** will be measured
- **Triplicate ECG** will be performed
- **Blood sample** will be collected for routine laboratory safety tests. You will be provided with a pathology form for Clinical Labs Australia. Clinical Labs is located adjacent to the Australian

Alzheimer's Research Foundation. Please ensure that you fast from food for at least 8 hours prior to your arrival (consuming water is allowed).

- **Pregnancy Test:** If you are female and deemed by the study doctor to be capable bearing children, you will have a pregnancy test on weeks 15, 26, 52, 78 and 91 only.
- **Dispensing of Probucol (Lorelco™) or Placebo**: Your study treatment will be provided to you for at-home dosing at every visit. You will be provided with an amount to last until your next visit.
- **Dose administration:** One dose per day taken in the morning, with food. In the event that you miss a dose of medication, please take the capsule as soon as you remember. If more than 2 hours have passed since you were due to take the capsule, do not take the capsule that you missed. Resume taking the capsules as per usual at the next scheduled time. Do not double dose (take two capsules at once) if you have missed a dose. This may increase the chance of experiencing any side effects.
- **Adverse Reactions:** You will be monitored to check for any reactions to the dose and will be questioned about your health routinely throughout the day. Any other medications that you use will also be recorded.

Telephone Calls (weeks 6, 20, 29, 47, 55, 73, 81)

Study staff will conduct a number of follow-up telephone calls to each participant during this period. During the call the clinical staff member will discuss with you your general health and ask for any medication you may have taken during this period. The study staff may also ask to speak to your study partner.

End of Study (Week 104)

The duration of the end of study visit is approximately 3 hours, however some of the tests may take place on a different day. During your appointment(s) you will be offered regular breaks and refreshments. The following procedures will be performed during your last visit to the clinic:

- **Review of medications used**
- **Full physical exam** will be conducted
- **Vital signs** will be measured
- **Triplicate ECGs** will be conducted
- **Blood sample** will be taken for routine laboratory safety tests. You will be provided with a pathology form for Clinical Labs Australia. Clinical Labs is located adjacent to the Australian Alzheimer's Research Foundation. Please ensure that you fast from food for at least 8 hours prior to your arrival (consuming water is allowed).
- **Assessment of Alzheimer's Disease:** You will be asked to undergo a PET/MRI scan. This may take place on a different day to the other tests. You (and your study partner) will also undergo a number of assessments in which the investigator will assess a range of mental functions.

Follow-Up (Week 108)

The following procedures will be performed during your last visit to the clinic. This visit will last approximately 1 hour.

- **Medical review** of your general health will be conducted and a physical exam may be performed if you are not feeling well, or your Study Doctor determines an examination is required.
- **Review of medications used**
- **Vital signs** will be measured
- **Triplicate ECG** will be performed

- **Blood sample** will be collected for routine laboratory safety tests. You will be provided with a pathology form for Clinical Labs Australia. Clinical Labs is located adjacent to the Australian Alzheimer's Research Foundation. Please ensure that you fast from food for at least 8 hours prior to your arrival (consuming water is allowed).

Early Termination Procedure

In the event that your participation in the study ends prior to the planned week 104, you will be asked to attend the clinic for the following procedures to be performed:

- Full physical exam will be conducted
- Vital signs will be measured
- Duplicate ECG will be conducted
- **Blood sample** will be collected for routine laboratory safety tests.

This visit will last approximately 1 hour.

In the event that you require follow-up appointments due to any changes in your health during the study, you will be required to be available for follow-up until these changes return to normal, at the discretion of the study doctor.

Blood Sampling

Over the course of the study blood samples will be taken approximately 13 times. All blood samples will be collected via venepuncture.

The total volume of blood taken for the entire study will be approximately 200 mL over two years. A standard blood donation is 470 mL in any 12-week period. You are advised not to donate any additional blood for 12 weeks after completing the study. As with all studies requiring blood donations, adequate rest and good eating habits are also advisable.

STUDY PERIODS►	Screening	PRE-BASELINE-Visit 0	BASELINE Visit 1																	
OUTPATIENT VISIT►	X	X	X	X	X		X		X		X		X		X		X		X	X	X
TELEPHONE CALL►						X		X		X		X		X		X		X			
STUDY DAY►	Day -24 - Day-1	Week 1-Week 3	Week 3 Day1	Week 4	Week 5	Week 6	Week 15	Week 20	Week 26	Week 29	Week 39	Week 47	Week 52	Week 55	Week 65	Week 73	Week 78	Week 81	Week 91	Week 104	Week 108
WINDOW►		± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	± 2 Days	±2 weeks
Informed Consent	X																				
Incl. Excl Criteria	X	X	X																		
Demographics	X																				
Medical & Disease History	X																				
Other Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment History	X																				
Physical Examination[1]	X			X	X		X		X		X		X		X		X		X	X	X
Vitals	X			X	X		X		X		X		X		X		X		X	X	X
ECG	X		X	X	X		X		X		X		X		X		X		X	X	X
Pregnancy Test	X		X				X		X				X				X		X		
Blood samples[2]	X		X	X	X		X		X		X		X		X		X		X	X	X
Disease marker genetic testing	X																				
Global Memory Task[3]	X																			X	
Recall Task[4]	X																				
CDR Memory Rating Task[5]	X																				
Memory & Thinking Task[6]			X								X+		X				X+			X	
DASS-21 Mood Questionnaire[7]		X							X											X	
ADCS-MCI-ADL24 Daily Activities Questionnaire[8]		x							X											X	
PET scan/MRI	X																			X	
Dispense study drug	X	X	X	X	X		X		X		X		X		X		X		X		
Take study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug compliance check	X		X	X	X		X		X		X		X		X		X		X	X	
Reporting Adverse Reactions	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Overall Schedule of Assessments

Note. EOS = End of Study

[1] = Physical Examination includes physical and neurological assessment

[2] = Blood Samples includes Full Haematology and Biochemistry panel

[3] = Mini-Mental State Examination (MMSE),

[4] = Free and Cued Selective Reminding Test (FCSRT),

[5] = Clinical Dementia Rating (CDR)
[6] = AD Memory Tests includes Alzheimer's Disease Assessment Scales-Cognitive Subscale test (ADAS-Cog),
[7] = Depression, Anxiety, and Stress Scale -21 (DASS-21)
[8] = Alzheimer's Disease Co-operative Study Mild Cognitive Impairment Activities of Daily Living (ADCS-MCI-ADL24)

5 What other options do I have?

If you choose not to participate, are not eligible to participate, or withdraw from this study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled. If you do not (or cannot) participate, there are a number of options available to you, which you should discuss with the doctor treating your Alzheimer's. These may include:

- Participation in another study
- To receive standard treatment for your Alzheimer's Disease.

6 Who is conducting and paying for this research?

This research study is being conducted by the Australian Alzheimer's Research Foundation, on behalf of Curtin University who are paying for the study.

7 What if something new comes up during the trial?

We will tell you about it.

Occasionally, we find out something new about the study drug or one of the study procedures while the study is under way. If this happens, the study doctor will discuss these new findings with you and what they mean in relation to your participation in this study. Your wish to continue your participation in the study following the knowledge of the new findings will be discussed. If you decide to withdraw, the study doctor will make arrangements for discontinuation of your participation in this study. If you decide to continue in the clinical trial we will ask you to sign an updated consent form.

8 Could the researchers stop the trial early?

Yes, it happens sometimes. If it does, the study doctor will let you know and explain the reason behind the decision. This research project may be stopped unexpectedly for a variety of reasons. Some possibilities include:

- The study drug is shown not to be effective
- Decisions made by local regulatory/health authorities
- Unacceptable side effects
- You need additional medication
- You become pregnant or begin breast-feeding
- You do not consent to continue in the research project after being told of changes in the research that may affect you, or for any other reason.
- If you no longer have (and cannot find a replacement) study partner.

9 What will happen to the confidential information about me?

We will keep any information confidential and securely stored. We will use and retain information that we collect about you only for this clinical trial. We will not disclose your information without your permission, except in compliance with the law.

All of the data collected about you will be coded. No personal information about you, such as your name and address will leave the study site and in all study information sent out from the clinic you will be identified with a unique study code only. The key to the code will be securely stored by the Trial Coordinator at the study site.

10 What information will be collected, and how will it be stored?

Your records relating to this study and any other information received will be kept strictly confidential. However, staff participating in your care, the Sponsor and its authorised representatives, and other agencies authorised by law, may inspect the records related to the study. In the event you are admitted to hospital as a result of a side effect resulting from this study, your treating doctor may require access to your study records.

Unless required by law, only your Study Doctor, the study team, the Sponsor and its authorised representatives, the Therapeutic Goods Administration (TGA), health authorities from other countries where the study drug may be considered for approval and Bellberry Human Research Ethics Committee will have access to data: which identifies you by name, from which your identity is otherwise apparent or which can be reasonably ascertained.

Your identity will not be revealed, and your confidentiality will be protected in any reviews or reports of this study which may be published. However, results may be suppressed for commercial reasons as the Sponsor of the project retains the rights to the data.

Your General Practitioner will be notified of your participation in this study and of any clinically relevant information noted by the Study Doctor in the conduct of the study. All personal information will be used only for the purpose of administering your participation in this study and in accordance with the laws governing the protection and privacy of personal information under Australian privacy legislation.

Australian privacy laws give you the right to request access to your information that the researchers have collected and stored. The law also gives you the right to request corrections to any information about you that you disagree with. Please contact the site study team (contact details listed at the end of this document) if you would like to access your information. Participants should note that some data derived from your participation in this study will be sent overseas; the regulatory regimes governing data access and use in other countries may not be the same as those that are in place in Australia. If you have any questions about this direct them to the Study Doctor. By signing the Consent Form, you authorise release of and access to this confidential information to the relevant study personnel and regulatory authorities as noted above.

All of your collected information will be kept by the Study Doctor for at least 15 years after the end of the study. The Sponsor may decide that the study records need to be kept longer. Once the study records are no longer required, your identifying information at this Institution will be permanently deleted from the computer system and any hard copies will be destroyed.

11 What are my responsibilities during the trial?

If you agree to participate in this study, you agree to be responsible for participating in study procedures according to our instructions. You also agree to comply with the other conditions in this document. If you cannot, or do not wish to accept this responsibility, then we cannot accept you as a participant in the trial.

If you decide to take part in this study, you will be required to attend the Australian Alzheimer's Research Foundation for a total of 14 visits (although this may vary slightly depending on availability of MRI/PET scan equipment). You will also be required to be available for discussions by telephone as required. You should consider if you are able to meet this time requirement.

If you decide to take part in this study, you will be required to adhere to the following restrictions:

- You will be required to fast for at least 8 hours prior to each safety blood sampling during screening and study weeks 3, 4, 5, 15, 26, 39, 52, 65, 78, 91, 104 and 108. Water is permitted though;
- You must not take prescription or non-prescription medication that may affect electrical activity of the heart within 7 days prior to the study drug administration and throughout the study, unless approved by the study investigator;
- You must not have participated in another investigational clinical trial within 90 days prior to study drug administration;
- Female participants of child-bearing potential, must agree not to attempt to become pregnant, must not donate ova, and must use highly effective method of contraception between signing the consent form until at least 30 days after the last dose of study therapy;
- Male participants, if not surgically or biologically sterilised, must agree not to donate sperm and if engaging in sexual intercourse with a female partner who could become pregnant, must agree to

use a highly effective method of contraception between signing the consent form until at least 90 days after the last dose of study therapy.

12 What possible benefits might I get by taking part?

In this study, half the participants will get study drug and half will get placebo. We cannot guarantee or promise that you will receive any benefits from participating in this study as the study drug may or may not help your AD. It is possible that you will receive no direct health benefit from being in this study.

13 What risks do I run by taking part?

Medical procedures, medicines and tests often have side effects. You may have no side effects, some or all of the side effects listed below. These side effects may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your Study Doctor. Your Study Doctor and the site study staff will also be looking out for side effects.

There may also be side effects that the researchers do not expect or do not know about and that may be serious. Tell your Study Doctor immediately about any new or unusual symptoms that you get.

Since there is always the possibility that some unexpected adverse effects may develop in some people who take this drug, trained medical personnel are available at the study site for immediate medical attention. At regular intervals throughout the study you will be questioned about how you are feeling. If you experience any unusual signs or symptoms, you should report them to the Study Doctor as soon as possible. The Study Doctor has the right to withdraw you from the study at any point for medical reasons.

Many side effects go away shortly after the treatment or procedure ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your Study Doctor may need to stop your treatment. Your Study Doctor will discuss the best way of managing any side effects with you. Some unwanted effects may actually not be related to the study, nevertheless it is important to document these.

Risks Associated with Probucol

Probucol (Lorelco™) has been extensively evaluated in humans and continues to be prescribed in multiple countries for heart-related diseases. Because of this, we have information on the side effects that may be seen in humans.

The majority of side effects of probucol are well documented (see Table 2). Some subjects may experience fast or irregular heartbeat, diarrhea or nausea which is usually temporary, stomach cramps, swelling of the abdomen, dizziness, or vomiting. In rare instances, subjects may experience swelling on face, hands, or feet, or in mouth, unusual bleeding or bruising, unusual tiredness or weakness.

Table 2. Potential side effects of Probucol (Lorelco™)

Organ	Common (0.1% - < 5%)	Rare (<0.1%)
Gut	[+]Diarrhoea or loose stools, [+]Build up of gas, [+]Abdominal pain, [+]Nausea, [+]Vomiting, [+]Indigestion,	Gastrointestinal bleeding
Heart	Abnormal electrical activity of heart , Abnormal heart rhythm, Abnormal heart rate	
Nerves	[+] Headache, [+] Dizziness,	Abnormal sensation of the skin, Sleep problems, Ringing of the ears, Nerve damage

Blood		Alterations to red blood cells,
Skin	+ Rash, + Skin irritation, + Bruising, + Increased sweating,	
Sexual and urinary	Erectile dysfunction, Increased waking to urinate	
Eyes	Blurred vision, Reddening of the lining around the eye	
Hormonal	Enlargement of Thyroid	
Reactions to food or drugs	+Nausea, +Vomiting, + Dizziness, Heart racing	
Other	+ Diminished sense of taste and smell	Skin swelling

+ If experienced, these tend to have a less severe expression

Because of the information we have on the human side effects of Probucol, the screening assessments to determine whether you are eligible, are being performed to ensure that your body systems are functioning at a level suitable for you to be given the study drug and also act as a baseline measure to compare your future results. Should you be considered as suitable, and wish to participate in the study, your Study Doctor will be monitoring you closely and **you need to tell your Study Doctor or a member of the site study team immediately if you experience any side effects.**

In addition to potential side effects from the study drug, there are risks associated with procedures performed during the study. These risks are described below:

Blood Draw Risks

You may have pain or bruising at the site where blood is drawn, although this is generally minor and resolves within a few days. There is a small risk that a clot will form in the vein, which may take a number of weeks to resolve. An infection at the site of blood draws or cannula insertion is also possible although the use of antiseptic solutions prior to the drawing of blood minimises this risk. Procedures relating to blood drawing can also occasionally cause light-headedness or fainting. These reactions are usually mild, of short duration and limited to a feeling of weakness, accompanied by sweating, slowing of heartbeat, and a decrease in blood pressure.

ECG

As a result of the patches that are put on your skin when performing the ECG, there is the possibility a rash or minor irritation of the skin may result.

MRI

MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room. We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker or metal pins.

PET scan

There are minimal risks associated with the PET/CT imaging that may cause minor side effects. To minimise any risk, you will be under the care of a Nuclear Medicine physician whilst undergoing the scan. The amyloid tracer will be injected by a trained Nuclear Medicine nurse or a Nuclear Medicine technologist and the imaging is supervised at all times by trained Nuclear Medicine technologists, nurses and doctors. The camera is a donut shape, like a CT scanner. Occasionally some patients feel claustrophobic or 'closed in'

when they are under the camera, this may cause breathing and heart rate to become faster, and some people may become sweaty or feel anxious. This feeling should disappear once the scan is finished. If you are concerned you may develop these symptoms, please discuss this with us prior to having the scan.

Complications related to insertion of the intravenous catheter (IV line) used to give the PET tracer can occasionally occur. These mainly involve pain, slight bruising and, very infrequently, infections can occur. Additionally, as you are required to fast prior to the PET scan, you may feel dizzy, lightheaded, and/or fatigued. You will be given appropriate treatment at the hospital if a reaction or complication occurs.

Reproductive risks

It is important that female participants in this study are not pregnant or breast-feeding and do not become pregnant during the course of the study.

For women:

You must confirm to the Study Doctor that, to the best of your knowledge, you are not pregnant now, and that you do not intend to become pregnant during the study.

Female participants of childbearing potential must have a negative pregnancy test at screening and before the first Probucol (Lorelco™) administration (Day 1 urine test, blood test if positive urine test is found). Women are considered to be of childbearing potential unless they have gone through menopause, which is defined as 12 months with no periods, without any medical condition that would otherwise explain the absence of periods; or are surgically sterile by the removal of the uterus (hysterectomy), both ovaries (bilateral oophorectomy), or both Fallopian tubes (bilateral salpingectomy) at least 6 weeks prior to screening. Post-menopausal status will be checked by measuring hormones in the blood at screening.

Women of childbearing potential must agree not to attempt to become pregnant, must not donate ova, and must use at least one form of highly effective contraception/birth control, from the time of signing this consent form until least 1 month after the last dose of Probucol. You should discuss methods of highly effective contraception with your Study Doctor.

Contraceptives considered highly effective are:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Sterilised male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence: When this is in line with your preferred and usual lifestyle.

Examples of non-acceptable methods of contraception include:

- Condoms alone or double barrier.
- Periodic abstinence (e.g. calendar, ovulation, sympthothermal, post ovulation).
- Withdrawal

In Australia, spermicide is not approved as a method of contraception and is not considered highly effective.

If you are uncertain of what form of contraception is acceptable for use during the study, please ask the Study Doctor.

If you suspect that you have become pregnant during the study, you must notify the Study Doctor immediately. You will not be able to continue participation in the study if you become pregnant. In the event you become pregnant during the course of the study, you will be immediately withdrawn from any ongoing study treatment. A separate consent form will be provided to you to sign to allow the Study Doctor access to medical information to allow monitoring of the pregnancy, and the birth and the health of the child up to one year of age.

For men:

If you are male, you should not father a child or donate sperm during your participation in this study and for at least 3 months after the last dose of Probucol. Male participants who have not previously been surgically sterilised must use a condom in addition to having their female partner use an effective contraception method from signing this consent form until at least 3 months after their last dose of Probucol. You should discuss methods of highly effective contraception with your Study Doctor.

It is also highly recommended that you inform your partner of your participation in this study and that contraception is required. If you or your partner become pregnant whilst participating in the study, you should advise your Study Doctor immediately. Your Study Doctor will advise on medical attention for you or your partner should this be necessary. A separate consent form will be provided to you/your pregnant partner to sign to allow the Study Doctor access to medical information to allow monitoring of the pregnancy, and the birth and the health of the child up to one year of age.

Non-physical risks

Because of side effects or the time required for tests and clinic visits while you are participating in this study, you may be unable to keep up with your normal daily activities.

14 How will you use any tissues or samples you take from me?

If you agree to participate in this trial, we will collect blood and urine samples. Your blood and urine samples will be used for routine medical tests, and to identify the substances that may be produced when the body breaks down or metabolises Probucol. This type of testing is done to ensure your health and safety throughout your participation in the trial. You will not be informed of the results of the tests, unless the Study Doctor deems you are unable to continue in the study.

The blood and urine samples collected at clinic visits are a mandatory part of the study. They are for research purposes only and will be analysed at laboratories that are located in Australia. Only authorised study staff and laboratory staff will have access to your samples and the results. The blood and urine samples collected for safety analyses will be stored at the laboratory conducting the analysis until after the end of the study and will be destroyed, after they are analysed. The samples will be coded with the unique study code assigned to you and will therefore be non-identifiable. Research samples of blood will be stored for a minimum of 7 years at Curtin University. Optional genetic samples will be stored for 15 years. All specimens, samples and medical images (MRI and PET scan images) obtained from you during this study will be used and kept for research purposes.

Signing the Consent Form means that you agree to have this testing; it will not be done without your consent.

If you withdraw your consent to participate in this study, you are entitled to request that all collected samples are destroyed, to prevent further analysis.

Will you be doing any genetic tests?
Yes. Genotyping for Apolipoprotein E (ApoE ε4) will be collected to look for ApoE ε4, a gene that influences your risk of developing AD. You will not receive the result of this test during the study, however, you may request access to the result at the end of the study.

15 What happens if I am injured as a result of my participation in this trial?

If you suffer any complications as a result of this study, please contact us as soon as possible (see Section 21 for study contact details).

In case of an emergency, contact 000.

If you are injured as a result of your participation in this study, you may be entitled to compensation. Sponsors of clinical studies in Australia have agreed that the guidelines developed by their industry body, Medicines Australia, will govern the way in which compensation claims from injured participants are managed by Sponsors. However, as guidelines, they do NOT in any way dictate the pathway you should

follow to seek compensation. The Sponsor is obliged to follow these guidelines. These guidelines are available for your inspection on the Medicines Australia Website (www.medicinesaustralia.com.au) under Policy – Clinical Trials – Indemnity and Compensation Guidelines. Alternatively, a member of the site study team can provide you with a hard copy of the guidelines.

It is the recommendation of the Human Research Ethics Committee responsible for the review of this study that you seek independent legal advice before taking any steps towards compensation for injury.

16 Will you pay me to participate in this trial?

You will not be paid for participating in this study.

17 Are there any costs associated with my participation?

You will be required to pay for your parking at the Australian Alzheimer's Research Foundation. Payment machines are located in the carpark at the study site and you will be required to display your ticket on your car dashboard. You will, however, be reimbursed for all parking expenses associated with participating in this trial. You will be required to provide a receipt as proof of payment to the trial coordinator.

18 Can I have other procedures during this clinical trial?

No, you should not undertake any other medical procedures or take any other medications whilst you are a participant, unless reviewed and approved by the study investigator. You must tell us about any procedures or medicines you may be taking. This is in your interest as well as important for the trial. You must tell us about any over-the-counter medications, vitamins or herbal remedies and about nutritional supplements because they may interact or interfere with the study drug. You must also tell us about any changes to these while you are participating in the clinical trial.

19 What happens when the trial ends?

The study medication will not be available to you after the study ends. If you have any medical conditions that continues beyond the end of the study the study doctor may arrange for follow up visits, safety tests (which may include blood and/or urine tests), or telephone calls until this condition resolves or becomes stable.

20 Will the results of the trial be published?

The Study Doctors and/or the Sponsor may decide to discuss or publish the results of the study. This communication may include publication in peer-reviewed journals, presentation at conferences or other professional forums. In any publication, information will be provided in such a way that you cannot be identified. You may request a copy of the study results from your Study Doctor if you wish.

A description of this study will be available on a publicly listed register, www.anzctr.org.au. This website will not include information that can identify you. You can search this website at any time.

To protect your privacy, no information will be published that could identify you as a participant in this study. The intention of this study is to gather data however the data will be de-identified. This may take some time and should be discussed with the Study Doctor.

21 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC) who make sure that the rights and safety and well-being of human subjects in a study are protected.

Bellberry HREC has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2007) incorporating all updates. This statement has been developed to protect the interests of people who agree to participate in human research studies.

22 What if I have a question or need to make a complaint or seek compensation for injury?

We have included several contacts for you below. Who you contact depends on what information you need.

Emergency Information: In case of medical emergencies during the study you should first ring **000** to receive immediate medical assistance. If it is not a medical emergency, or if you have any urgent questions concerning discomfort or injury associated with the study, please telephone the numbers below.

For all study enquiries or if you want to talk to the study team at any time:

Emily Corti: 0431 584 166

Associate Professor Roger Clarnette:

- **After hours telephone: 0415 956 611**
- **Email: Roger.Clarnette@health.wa.gov.au**

If you experience any side-effects or complications as a result of this clinical trial, you should contact the study team as soon as possible. They will arrange appropriate medical help.

If you wish to discuss the study or with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you **may** contact:

Reviewing HREC name	Bellberry Human Research Ethics Committee
HREC Executive Officer	Operations Manager
Telephone	**08 8361 3222**
Email	Bellberry@bellberry.com.au

23 The consent form

Sign the consent form only after you have made up your mind to take part in this study. If you wish, we will arrange for someone to read the form to you in a language you understand. You must be provided with a signed and dated copy of the Participant Information Sheet and Consent Form for your personal record.

Consent Form

Title	A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition		
Protocol number	PIA-2020		
Project sponsor	Curtin University		
Principal investigator	Associate Professor Roger Clarnette		
Clinical contact person	Emily Corti	0431 584 166	
24-hour medical contact	Roger Clarnette	0415 956 611	Roger.Clarnette@health.wa.gov.au

Note: All parties signing the consent section must date their own signature.

Declaration by participant

- I have read, or have had read to me, and I understand the General Information PICF as well as this Participant Information Sheet and Consent Form.
- I have had the opportunity to have a member of my family or another person present while the study is explained to me.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this study as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand the purposes, procedures and risks of the research described in this Participant Information Sheet. Although I understand that the purpose of this study is to improve the quality of medical care, it has also been explained to me that my involvement may not be of any direct benefit to me.
- I understand that access may be required to my medical records for the purpose of this study as well as for quality assurance, auditing and in the event of a serious adverse event. I understand that such information will remain confidential.
- I understand that I will be randomised to either the Probucol (Lorelco™) or Placebo group, and that neither I nor the Study Doctor will know which group I am in.
- I understand and agree to my study partner providing information about my health to the Study Doctor.
- I consent to my local doctor being notified of my participation in this study and any clinically relevant information noted by the Study Doctor in the conduct of the study.
- I agree to adhere to the protocol requirements and restrictions as laid out in this Participant Information Sheet.
- I understand that I must use adequate contraception during the study. In the event of myself or my partner becoming pregnant, I must inform the Study Doctor immediately.
- I am 18 years of age and under 85 years of age.
- I understand that I will be given a signed copy of this document to keep.

Signature	_____	Date_____	Time_____
Name of participant (please print)	_____ First, Middle Name or Initial, Last (must be as per photo ID)		

Declaration by trial doctor

I have given a verbal explanation of the clinical trial, its procedures and risks and I believe that the participant has understood that explanation.

Signature	_____	Date_____	Time_____
Name of trial doctor (please print)	_____		

Withdrawal of Consent form

Title	A Double-Blind, Placebo Controlled, Randomised Phase II Trial of Probucol in Alzheimer's Disease (PIA-Study): The Impact on Cognition		
Protocol number	PIA-2020		
Project sponsor	Curtin University		
Principal investigator	Associate Professor Roger Clarnette		
Clinical contact person	Emily Corti	0431 584 166	
24-hour medical contact	Roger Clarnette	0415 956 611	Roger.Clarnette@health.wa.gov.au

Note: All parties signing must date their own signature.

Declaration by participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Australian Alzheimer's Research Foundation. I hereby wish to:

Option 1: Withdrawal from the study completely

I wish to withdraw from the study completely

OR

Option 2: Withdrawal from treatment only:
I wish to discontinue protocol treatment only but will continue study follow-up procedures/assessments via:

Australian Alzheimer's Research Foundation visits

Telephone follow-up with me

Continued collection and use of blood and urine samples during follow-up

Signature	_____	Date_____	Time_____
Name of participant (please print)	_____ First, Middle Name or Initial, Last (must be as per photo ID)		

Declaration by trial doctor

I have given a verbal explanation of the implications of withdrawal from the clinical trial and I believe that the participant has understood that explanation.

Signature	_____	Date_____	Time_____
Name of trial doctor (please print)	_____		